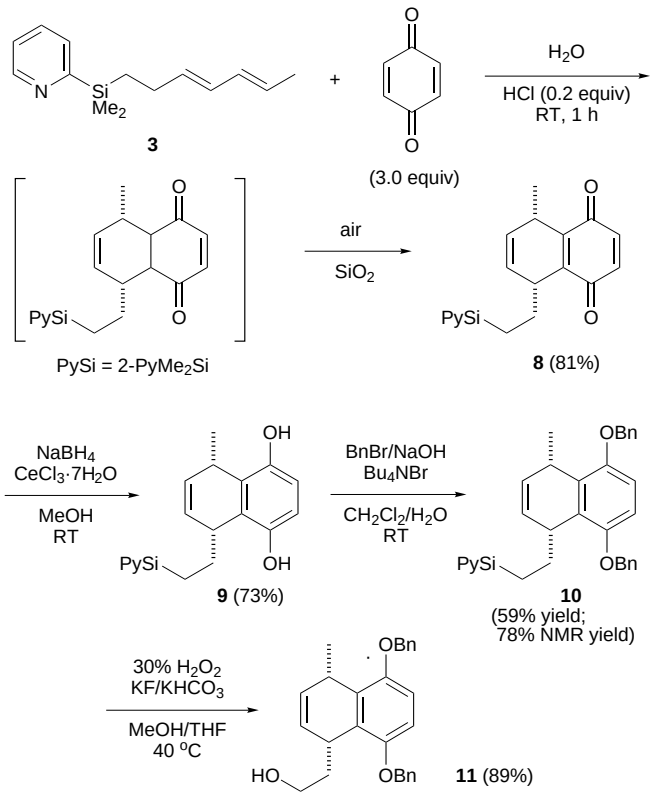

Scheme 1. Aqueous Diels–Alder reaction of **3** and removal of the 2-$PyMe_2Si$ group. Bn = benzyl.

fected throughout these transformations, which indicates the reasonable chemical stability of this group. Finally, the oxidation of **10** with H_2O_2 afforded **11** in 89% yield without affecting the C–C double bond or eroding the stereochemistry at the allylic carbon atoms.

In summary, we have demonstrated the "proof-of-principle" of our strategy for aqueous organic reactions by utilizing the 2-$PyMe_2Si$ group as a removable hydrophilic group. Importantly, the strategy described herein should not be limited to aqueous Diels–Alder reactions but could in principle be applied to other aqueous organic reactions as well.

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The Combination of Spontaneous Resolution and Asymmetric Catalysis: A Model for the Generation of Optical Activity from a Fully Racemic System**

Olivier Tissot, Maryse Gouygou,* Frédéric Dallemer, Jean-Claude Daran, and Gilbert G. A. Balavoine*

Dedicated to Professor Henri Kagan on the occasion of his 70th birthday

Considerable efforts have been devoted to the development of new chiral ligands owing to the growing importance of transition metal catalyzed asymmetric synthesis.[1] Among these chiral ligands, diphosphanes have played a dominant role, in particular those possessing C_2 symmetry.[2] We were interested in the possibilities offered by 1,1′-diphenyl-3,3′,4,4′-tetramethyl-2,2′-biphosphole (**1**) (BIPHOS), first synthesized by Mathey et al. in 1986.[3] This diphosphane combines the axial chirality generated by the biphosphole framework with the central chiralities of the phosphorus atoms. This implies the existence of six stereoisomers, corresponding to three pairs of enantiomers, which are in a fast equilibrium in

[*] Dr. M. Gouygou, Prof. G. G. A. Balavoine, Dr. O. Tissot, Dr. J.-C. Daran
Laboratoire de Chimie de Coordination du CNRS
205, Route de Narbonne, 31077 Toulouse Cedex (France)
Fax: (+33) 5-61-55-30-03
E-mail: gouygou@lcc-toulouse.fr, balavoin@lcc-toulouse.fr
Dr. F. Dallemer
Rhodia Recherches, Centre de Recherche de Lyon
85, Avenue des Freres Perret, BP 62, 69192 Saint-Fons Cedex (France)

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solution because of the configurational instability of the axial chirality and of the central chiralities of the phosphorus atoms.[4] This stereolability is overcome in the solid state, and the stereoisomers have been fully characterized by an X-ray diffraction study.[4] Herein we report the spontaneous resolution of the BIPHOS ligand by crystallization, the synthesis of the enantiomerically pure palladium complex [$PdCl_2$(biphos)], and its catalytic activity towards asymmetric allylic substitution.

The BIPHOS ligand **1** crystallizes as a conglomerate; each enantiomer crystallizes independently but no differences between these enantiomeric crystals are visible to the naked eye. X-ray diffraction studies of different single crystals[4, 5] allowed the relative and absolute stereochemistry of the two enantiomers to be determined, corresponding to *S*[*RR*] or to *R*[*SS*].[6] Single crystals of a rather large size (typically 50 to 150 mg) (Figure 1) were obtained and were used in the

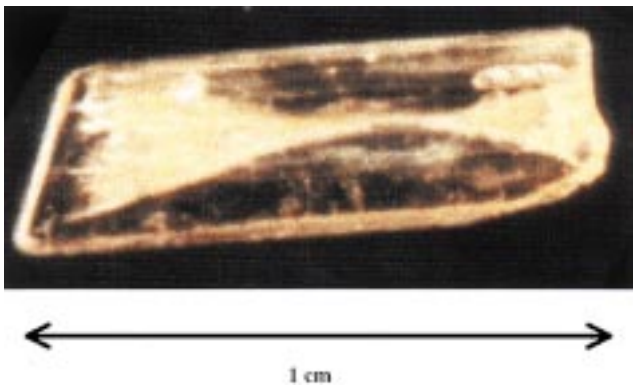
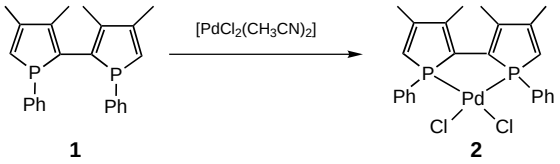


Figure 1. Photograph of a single crystal (150 mg) of compound **1**.

synthesis of the optically pure complex [$PdCl_2$(biphos)]. Before every reaction, the purity of each crystal was checked by polarized light. To prevent the racemization that occurs at $-60\,^{\circ}C$,[4] the reaction of a pure single crystal of **1** with one equivalent of [$PdCl_2(CH_3CN)_2$] (Scheme 1) was carried out at



1 **2**

Scheme 1. Synthesis of complex **2**.

$-78\,^{\circ}C$ in dichloromethane for 16 h. The ^{31}P NMR spectrum of the reaction mixture, measured at room temperature, exhibited only one sharp singlet at $\delta = 33.4$, indicating the quantitative formation of complex **2**.[7] This complex was isolated as a yellow solid in 93% yield with $[\alpha]_D^{20} = +200$ ($c = 0.02$ in CH_2Cl_2). Furthermore, the optical rotation of the solution remained unchanged after 24 h at $40\,^{\circ}C$, giving an indication of the configurational stability of complex (+)-**2**. Thus, the stereochemistry of BIPHOS ligand **1** is stable once it is coordinated to the metal. The enantiomeric purity of complex **2** has not been evaluated; however, starting from different single crystals of BIPHOS, the same absolute value of $[\alpha]_D$ was obtained for complex **2**. Furthermore, X-ray structure analysis of several single crystals of **2**, found in the same reaction mixture, show that they have the same absolute configuration. Therefore, we may consider that a single crystal of enantiomerically pure BIPHOS ligand in CH_2Cl_2 at $-78\,^{\circ}C$ reacts with [$PdCl_2(CH_3CN)_2$] to give the enantiomerically pure complex [$PdCl_2$(biphos)]. The molecular structure of complex (+)-**2**, which shows the *S*[*RR*][6] absolute configuration of the BIPHOS ligand, was determined by X-ray structure analysis[8] (Figure 2). All structural parameters, distances, and angles are similar to those of the racemic complex.[7]

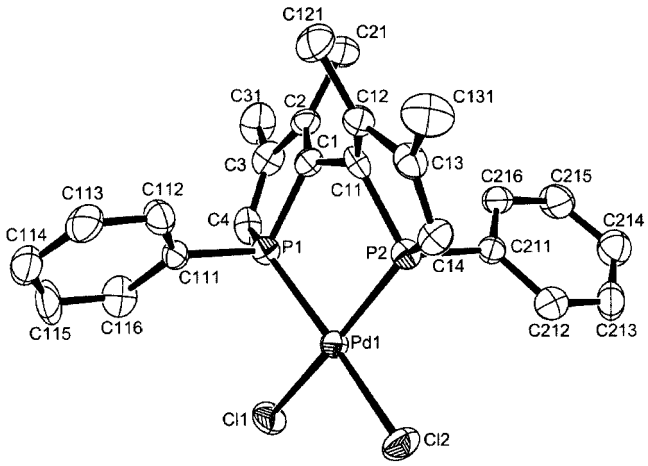
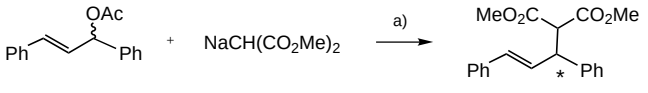


Figure 2. Molecular structure of *S*[*RR*]-(+)-**2** (ORTEP representation; the thermal ellipsoids correspond to 50% probability).

The enantiomerically pure palladium complex **2** was used in the catalytic asymmetric allylic substitution[9] of 1,3-diphenylprop-2-enyl acetate (**3**) with the anion of dimethyl malonate (Scheme 2). Our first study showed that a palladium complex



3 **4**

Scheme 2. Allylic substitution catalyzed by complex **2**. a) 1% [$PdCl_2$(biphos)].

generated in situ from [{Pd(η^3-C_3H_5)Cl}$_2$] and the racemic BIPHOS ligand proved to be a very efficient catalyst in dichloromethane at $35\,^{\circ}C$.[4] When complex *R*[*SS*]-(−)-**2** was used under the same conditions, the allylic acetate **3** was smoothly converted after 24 h into the desired product (*R*)-**4** in 84% yield and with 80% *ee* (Table 1, entry 1). However, the yield could be increased to 93% by using THF as solvent at $35\,^{\circ}C$, and even at a lower temperature ($25\,^{\circ}C$; Table 1, entry 2), without affecting the enantioselectivity. Furthermore, a similar experiment with the *S*[*RR*]-(+)-**2** complex gave the (*S*)-**4** product with the same yield (93%) and *ee* (80%, Table 1, entry 3). This again confirms the enantiomeric purity of complex **2**. The enantiomerically pure complex **2** prepared from a spontaneously resolved ligand proved to be

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Table 1. Asymmetric allylic substitution of 1,3-diphenylprop-2-enyl acetate with the anion of dimethyl malonate, using 1 mol% of the palladium complex **2**.

Entry	Catalyst	Solvent	T [°C]	Conversion [% of **3**][a]	*ee* [% of **4**][b]
1	*R*[*SS*]-(−)-**2**	CH_2Cl_2	37	84	80 (*R*)
2	*R*[*SS*]-(−)-**2**	THF	25	93	80 (*R*)
3	*S*[*RR*]-(+)-**2**	THF	25	93	80 (*S*)

[a] Evaluated by ^{1}H NMR spectroscopy. [b] Determined by HPLC analysis using a chiral column (Pharmacir 7C).

as effective as CHIRAPHOS,[10a] BPPF,[10b] DPPBA,[10c] and the BIPNOR[10d]/Pd^{II} system in the catalytic asymmetric allylic substitution of 1,3-diphenylprop-2-enyl acetate with the anion of dimethyl malonate (Table 1). Our results provide an interesting example of the spontaneous generation of optical activity from a racemic mixture by crystallization of a molecule that is stereolabile in solution, followed by amplification in an enantioselective catalytic process. The crystallization of chiral ligands or chiral catalytic complexes as conglomerates has already been described,[11] but to the best of our knowledge, the stereolabile BIPHOS ligand appears to be a special case. Because of the fast equilibrium between the two enantiomers in solution, the whole BIPHOS racemic mixture can be transformed into a single enantiomer,[12] giving the enantiomerically pure catalytic complex quantitatively.

Experimental Section

1: The biphosphole was prepared as described in the literature.[2b] To obtain single crystals, a very high purity of **1** is crucial. After purification by filtration through a short pad of silica gel (dichloromethane/pentane 70:30), the resulting oily residue was washed with pentane until a pale yellow solid was obtained. Subsequently, the slow evaporation of an undisturbed dichloromethane solution under argon gave single crystals of **1**.

2: A single crystal of BIPHOS **1** (0.050 mg, 0.13 mmol) was added to a stirred suspension of $[PdCl_2(CH_3CN)_2]$ (0.033 mg, 0.13 mmol) in dichloromethane (5 mL) maintained at −78 °C. The mixture was stirred at −78 °C for 16 h, and then warmed to room temperature and filtered. The slow addition of pentane to the solution gave complex **2** as an orange microcrystalline solid (0.067 mg, 93%), which was washed with pentane (2 × 2 mL). $[\alpha]_D^{20} = +200$ ($c = 0.02$ in CH_2Cl_2); ^{1}H NMR (CD_2Cl_2): $\delta = 1.87$ (d, $^4J_{P,H} = 2.9$ Hz, 6H; Me21, 121), 2.14 (d, $^4J_{H,H} = 1.5$ Hz, 6H; Me31, 131), 6.63 (m, 2H; =CH-P), 7.40–7.87 (m, 10H; Ph); ^{31}P NMR (CD_2Cl_2): $\delta =$ 33.4. Single crystals of *S*[*RR*]-(+)-**2** were obtained by the slow evaporation of a dichloromethane solution. Complex *R*[*SS*]-(−)-**2** was obtained in a similar way, starting from a single crystal of BIPHOS *R*[*SS*]-(−)-**1**.

General procedure for the allylic substitution: A solution of sodium dimethyl malonate resulting from the treatment of dimethyl malonate (0.148 mL, 1.29 mmol, 1.2 equiv) in THF (4 mL) with sodium hydride (80% NaH, 1.07 mmol) was added to a solution of complex **2** (7 mg, 0.0123 mmol) and 1,3-diphenylprop-2-enylacetate (310 mg, 1.23 mmol) in THF (2 mL). After 24 h at room temperature, the resulting mixture was diluted with diethyl ether (5 mL) and quenched with a saturated aqueous NH_4Cl solution (5 mL). The aqueous phase was extracted with diethyl ether, the combined organic phases were dried over $MgSO_4$, filtered, and evaporated to give the crude product, which was purified by chromatography (SiO_2, ethyl acetate/pentane = 15:85). The enantiomeric excess was determined by chiral HPLC using a Pharmacir 7C column, hexane/isopropanol (90:10), 0.7 mL min^{-1}, R_t for the *S* isomer = 13.84 min, R_t for the *R* isomer = 15.15 min.

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